Remarks

Applicants have herein amended claim 76. Support for the amendment to claim 76 can be found throughout the specification as filed. In particular, support for amended claim 76 can be found at, for example, within Table 1, page 327, row 2, indicated as cDNA clone HEMAE80, SEQ ID:310 (full-length and secreted polypeptide); at page 374, lines 3-7; and at page 365, lines 11-13. Thus, no new matter has been added.

Upon entry of the present amendment, claims 1-85 are pending in the application.

Rejections under 35 U.S.C. §§ 101 and 112, First Paragraph

The Examiner has maintained the rejection of claims 1-85 under 35 U.S.C. §101 because the claimed invention is allegedly "not supported by a specific and substantial asserted utility or a well-established utility." *See,* Office Action, page 3.Applicants respectfully disagree and traverse this rejection.

Contrary to the Examiner's allegations, the specification does in fact teach a utility for the claimed invention that satisfies the requirements of 35 U.S.C. § 101. Applicants respectfully point out that the instant specification discloses that the polypeptide of the claimed invention is preferentially expressed in the spleen, an organ that produces lymphocytes, filters blood and stores blood cells. *See e.g.*, Page 98, line 25 and page 99, line 26. Furthermore, the specification teaches that the claimed invention is useful in the treatment and/or diagnosis of specific hematopoietic disorders including anemia, pancytopenia, leukopenia and thrombocytopenia which are blood disorders characterized respectively by too few red blood cells, total blood cells, white blood cells and platelets. *See e.g.*, Page 99, lines 7-11.

Applicants contend that one of skill in the art would appreciate the central role of the spleen in hematopoiesis, the development of the cells of the blood involving both proliferation and differentiation from hematopoietic stem cells. Therefore, one of skill in the art would appreciate that the antibodies of the invention may be useful in the measurement of blood cell development in an individual and furthermore may be used in the treatment and/or diagnosis of a number of disorders associated with aberrant blood cell development including, for example, anemia, pancytopenia, leukopenia and thrombocytopenia.

Moreover, the teaching of exemplary methods, by which such a disorder may be detected using polypeptides of the invention, further supports the teachings of the specification. *See*, Example 22, page 430. Accordingly, Applicants assert that such

characterization of the invention is sufficient to constitute a showing of utility as required under 35 U.S.C. § 101.

Furthermore, the post filing publication of Liu *et al.* corroborates that, as first disclosed by Applicants, the claimed invention may be useful in the treatment and/or diagnosis of hematopoietic disorders including, for example, anemia, pancytopenia, leukopenia and thrombocytopenia. Applicants respectfully direct the Examiner's attention to the teachings of Liu *et al.*, *Genomics* (2000) 65:283-292 (cited as Reference AD, in Applicants' Information Disclosure Statement of December 20, 2001), and Krause *et al.*, *Blood* (1996) 87:1-13 (currently submitted herewith as reference BC in a Supplemental IDS). Liu *et al.* demonstrates that the polypeptide of the instant invention is specifically expressed in hematopoietic stem/progenitor cells (HSPC) that express the CD34 surface antigen ($CD34^+$) and can give rise to all the blood cells in the circulatory system.

Specifically, Liu *et al.* states that "[p]urified $CD34^+$ cells can engraft in bone marrow and generate blood/lymphoid cells for years in patients after transplantation," and that "cells that lack CD34 expression ($CD34^-$) are largely mature hematopoietic cells of various differentiated lineages. *See,* page 283, right column. Additionally, Krause *et al,* cited in the Liu *et al.* reference, teach that as early as 1996, CD34 was used "as a label for quantitation of stem/progenitor cells in blood and marrow, and as a target for immunologic purification of stem/progenitor cells for clinical transplantation." *See*, page 8, sentence bridging left and right columns.

Moreover, the post filing publication of Bazan *et al.* further corroborates the usefulness of the claimed invention in the treatment and/or diagnosis of hematopoietic disorders including, for example, anemia, pancytopenia, leukopenia and thrombocytopenia. Applicants respectfully direct the Examiner's attention to the teachings of Bazan *et al.*, United States Patent Application Publication No. US 2003/0082184 A1 (currently submitted herewith as reference BB in a Supplemental IDS). Bazan *et al.* describe the administration of polynucleotides and polypeptides of HEMAE80 to Rag2 x gc -/- mice that lack T cells, B cells and NK cells, and they describe how this treatment has profound effects on bone marrow composition and leads to significant increases in expression of hematopoietic cytokines including IL-6 and GCSF.

Specifically, Bazan *et al.* sacrificed mice treated using polynucleotides of the invention and collected bone samples for analysis by Hematoxylin and Eosin (HE) staining as well as by quantitative PCR. They showed "profound effects on bone marrow composition"

and "a 2.5 fold increase in the levels of IL-6 ... [in] HEMAE80 treated mice." *See*, page 18, lines 2 to 10. Moreover, Bazan *et al.* carried out a similar analysis on mice treated using polypeptides of the invention and demonstrated a greater than 2 fold increase in the hematopoietic cytokines IL-6 and GCSF. *See*, page 18, lines 18 to 19.

These reports clearly show that expression of the polypeptide of the instant invention is restricted to those hematopoietic cells that express CD34 and are capable of giving rise to all of the blood cells of the circulatory system, and that an effective method for the quantitation and/or identification of such $CD34^+$ cells has immediate clinical usefulness in the treatment and diagnosis of hematopoietic disorders. They also show that administration of polypeptides of the instant invention has profound effects on bone marrow composition and the expression levels of hematopoietic cytokines in an animal model used to study hematopoiesis and bone morphology. Accordingly, Applicants assert that these reports corroborate that the invention as claimed has utility as required under 35 U.S.C. § 101.

Applicants respectfully point out that the specificity of this asserted utility is not called into question by the alleged ability of other proteins to be used in a similar manner. A proper inquiry into utility is simply whether one of skill in the art would more likely than not find it specific, substantial and credible that compositions of the invention, which is preferentially expressed in the spleen, would be useful in the treatment and/or diagnosis of disorders of the blood as described above. Applicants note that an equation of the proper legal requirement of "specific utility" with a "unique utility" is improper. This is clearly not the legal standard for satisfaction of the requirements of 35 U.S.C. § 101. As described in detail above, the polypeptide of the present invention is preferentially expressed in $CD34^+$ hematopoietic cells, and therefore may be used specifically to measure levels of hematopoietic stem/progenitor cells in biological samples and treat and/or diagnose disorders associated with altered levels of such cells. Furthermore, administration of the polypeptide of the present invention in an animal experimental model used to study bone morphology and hematopoiesis leads to enhanced expression of hematopoietic cytokines, and therefore may be used specifically to treat and/or diagnose hematopoietic disorders associated with altered levels of such cytokines. Therefore, Applicants contend that the asserted utility is specific.

Indeed, the M.P.E.P. states that "[a] 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention." *See*, M.P.E.P. § 2107.01(I) at [2100-32]. Therefore, in light of the directions

of the M.P.E.P., Applicants contend that the treatment and/or diagnosis of specific disorders, using specific compositions, constitutes a utility that is "specific to the subject matter claimed" and not "applicable to the broad class of the invention." Accordingly, Applicants respectfully suggest that the Examiner's rejection of the instant claims is not soundly based, and request that it be reconsidered and withdrawn.

Applicants further contend that the specific utility of the instant invention in the treatment and/or diagnosis of disorders including anemia, pancytopenia, leukopenia and thrombocytopenia is also a substantial utility. The use of compositions of the instant invention in the treatment and/or diagnosis of such disorders would prove substantially useful and beneficial to people suffering from these and other related disorders. Accordingly, the claimed antibodies of the present invention have a substantial utility as required under 35 U.S.C. § 101.

The Examiner has further alleged that:

> SEQ ID NO:310 is a totally new, uncharacterized polypeptide with no well-established utility ... in view of the lack of any experimental data in the specification as filed ... is of unknown biological function and additional experimentation is required to determine what biological function this polypeptide has ... the proposed uses ... are simply starting points for further research and investigation into potential practical uses of the polypeptide and antibody that binds thereto.

See, Office Action, pages 4-5. Applicants respectfully note that this assertion is contrary to well established law. The Federal Circuit has recently stated with respect to the rejection of claims for lack of utility that:

> "It is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." Newman v. Quigg, 877 F.2d 1575, 1581, 11 U.S.P.Q.2D (BNA) 1340, 1345 (Fed. Cir. 1989); see also Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 U.S.P.Q. (BNA) 1137, 1140 (Fed. Cir. 1983) ("It is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). Furthermore, statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained.

In re Cortright, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). Likewise, according to the axiom of patent law, the utilities asserted for the instant invention do not depend on a proven disclosure of its biological activity. Rather, the issue is whether an asserted utility is more

likely than not true to one of ordinary skill in the art. As discussed in detail above, the polypeptide of the instant invention is preferentially expressed in $CD34^+$ hematopoietic stem/progenitor cells and stimulates increased expression of hematopoietic cytokines, and therefore it may be useful in the treatment and diagnosis of hematopoietic disorders including anemia, pancytopenia, leukemia and thrombocytopenia. Applicants respectfully contend that a nexus has indeed been made between the molecule of the instant invention, hematopoiesis and disorders such as anemia, pancytopenia, leukemia and thrombocytopenia. Accordingly, Applicants contend that the asserted utility in the treatment and/or diagnosis of hematopoietic disorders is entirely credible to one of ordinary skill in the art.

In light of the above facts, Applicants contend that the utilities asserted in the specification for the invention as presently claimed are specific, substantial and entirely credible to one of skill in the art. Accordingly, Applicants respectfully request that the rejection of claims 1-85 under 35 U.S.C. § 101 be reconsidered and withdrawn.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a specific, substantial and well-established utility. Therefore, the Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. Since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims 1-85 under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 1-75 and claims 76-85 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Specifically, the Examiner alleges that the claimed invention is not enabling because:

> the instant specification does not disclose a nexus between the expression of SEQ ID NO:310 with any particular disease state or condition and the specification does not teach or predict whether SEQ ID NO:310 would be overexpressed or underexpressed in a particular disease state such that an antibody, which specifically binds SEQ ID NO:310 could be predictably used for diagnosis and immunotherapy.

See, Office Action, page 6.

Applicants respectfully disagree and traverse this rejection.

Applicants respectfully point out that the enablement requirement of 35 U.S.C. § 112, first paragraph requires nothing more than objective enablement. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of § 112, unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support. *Staehelin v Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992), *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana* 34 USPQ2d 1437, 1441 (Fed. Cir. 1995).

In order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to practice the claimed methods without "undue experimentation." Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 443 F.2d 1386, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.* Furthermore, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). In the present case, the issue is not whether the specification provides proof that HEMAE80 is overexpressed or underexpressed in hematopoietic disorders including anemia, pancytopenia, leukemia and thrombocytopenia, but rather whether the uses involving the claimed antibodies that bind the HEMAE80 polypeptide of SEQ ID NO:310 can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art.

The Examiner alleges that one of skill in the art would not know how to use the claimed antibodies "absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective for diagnosis." *See*, Office Action, page 9. Applicants respectfully note that this requirement is contrary to well established law. See *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples ... More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments ...

Thus, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Given the teachings of the specification, it cannot be said that the invention as claimed is not enabled. In fact, "the [E]xaminer agrees that methods of making and using a diverse array of antibody types were routine for those of ordinary skill in the art and one of ordinary skill in the art would know how to use antibodies that bind the polypeptide of SEQ ID NO:310 in the assays disclosed in the instant specification." *See*, Office Action, page 6. One of skill in the art would be capable of routinely using such antibodies in the purification of HEMAE80 polypeptide, which has been shown to cause increased expression of hematopoietic cytokines and could be used in the treatment of a patient suffereing from anemia, pancytopenia, leukemia and thrombocytopenia. Moreover, the skilled scientist, enlightened by the teaching of the present specification is more than capable of routinely determining whether antibodies, encompassed by the claimed methods is useful, for example, in binding a decreased amount of HEMAE80 in a sample from a patient suffering from anemia, pancytopenia, leukemia and thrombocytopenia and therefore would be expected to be useful according to the claimed methods.

In light of the state of skill in the art on the effective priority date of the present application, nothing more than routine experimentation would be required to practice the claimed methods ("[e]nablement is not precluded by the necessity for some experimentation

such as routine screening" (*See In re Wands*, 858 F.2d 731; 8 U.S.P.Q.2d (BNA) 1400), and "the key word is 'undue' not 'experimentation.'" (*See In re Angstadt*, 537 F.2d at 504; 190 U.S.P.Q. at 219)). Therefore, the skilled scientist, enlightened by the teaching of the present specification, is more than capable of routinely determining whether an antibody encompassed by the claims has uses commensurate in scope with the instant claims.

Thus, Applicants submit that due to: (1) the availability of routine methods for generating antibodies; (2) the availability of routine techniques for detecting the presence of specific proteins; (3) the teachings discussed in detail above in response to the rejection under 35 U.S.C. § 101 that the polypeptide of the instant invention is preferentially expressed in $CD34^+$ hematopoietic stem/progenitor cells and may be useful in the diagnosis of specific hematopoietic disorders; and (4) the high level of skill in the field of immunology and molecular biology, one skilled in the art could routinely generate the claimed antibodies and determine whether any given biological samples contained a polypeptide of the invention and satisfy the limitations recited in the claims. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection to claims 1-75, and claims 76-85 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 76-85 Under 35 U.S.C. § 112, Second Paragraph

Claims 76-85 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite "for reciting 'Secreted Protein HEMAE80 expressed on the surface of cells' in claim 76." *See* Office Action, page 9.

In response, Applicants have amended claim 76 such that the isolated antibody binds to "Secreted Protein HEMAE80 purified from a cell culture." Thus, the objectionable language has been clarified. Accordingly, Applicants respectfully request that the rejection of claims 76-85 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 76-85 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 76-85 under 35 U.S.C. § 112, first paragraph for alleged lack of written description. In particular, the Examiner alleges that "the instant specification does not disclose that the HEMAE80 protein is expressed on the surface of cells nor does the specification provide adequate written description for any transmembrane domain(s) of the polypeptide of SEQ ID NO:310." See, Office Action, page 10.

Without acquiescing to the instant rejection, Applicants have herein amended claim 76, thereby obviating this rejection. Accordingly, Applicants request that the rejection of claims 76-85 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the instant application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425.

Respectfully submitted,

Date: February 25, 2005

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